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MINISTRY OF AGRICULTURE, FISHERIES AND FOOD

FOOD ADDITIVES AND CONTAMINANTS COMMITTEE REPORT ON SOLVENTS

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1966

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Food Additives and Contaminants Committee

The terms of reference of the Food Additives and Contaminants Committee are:

To advise the Minister of Agriculture, Fisheries and Food, the Secretary of State for Scotland, the Minister of Health, and as respects Northern Ireland, the Secretary of State for the Home Department, on matters referred to them by Ministers, in relation to food contaminants, additives and similar substances which are or may be present in food, or used in its preparation, with particular reference to the exercise of powers conferred on Ministers by Sections 4, 5 and 7 of the Food and Drugs Act, 1955 and the corresponding provisions in enactments relating to Scotland and Northern Ireland.

The members of the Food Additives and Contaminants Committee are:
Professor R. A. Morton, F.R.S., Ph.D., D.Sc., F.R.I.C. (Chairman).
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Joint Secretaries
E. Doling, Esq.
W. M. Shortt, Esq., O.B.E., M.Sc., F.R.I.C.

Pharmacology Sub-Committee

The terms of reference of the Pharmacology Sub-Committee are:

To advise, at the request of the Food Additives and Contaminants Committee or the Committee on Medical and Nutritional Aspects of Food Policy, on the hazard to health of the consumer, including toxicological and carcinogenic risk, arising from the presence of additives and contaminants in foods.

The members of the Pharmacology Sub-Committee are:

Professor A. Kekwick, M.A., M.B., B.Ch., F.R.C.P. (Chairman).
Professor E. Boyland, B.Sc., D.Sc., Ph.D.
Professor G. Brownlee, D.Sc., Ph.D., F.P.S.
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Secretary
W. M. Shortt, Esq., O.B.E., M.Sc., F.R.I.C.

The following were members of the Food Additives and Contaminants Sub-Committee of the Food Standards Committee which began the review on Solvents.

Professor R. A. Morton, F.R.S., Ph.D., D.Sc., F.R.I.C. (Chairman).
C. A. Adams, Esq., C.B.E., B.Sc., F.R.I.C., Barrister-at-Law.
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J. M. Ross, Esq., M.B., D.P.H.

The former Pharmacology Panel of the Food Additives and Contaminants Sub-Committee had the same membership as the present Pharmacology Sub-Committee except that Dr. F. J. C. Roe has replaced Mr. P. McGregor, B.Sc., F.R.I.C.

Remit

1. The Food Standards Committee was asked in December 1960 to review the use of solvents in food and to advise on the need for regulations. The Committee referred the question to its Food Additives and Contaminants sub-Committee. The sub-Committee requested evidence from interested parties and, when this was received, began its consideration of the problems involved. This consideration was not completed by November 1964 when the sub-Committee was abolished and replaced by the present Committee, which took over all its outstanding work. This report is, therefore, largely based on the work carried out by the sub-Committee.

Use of Solvents

2. Solvents are used in the food industry to dissolve, dilute, disperse and extract substances. Water is used wherever possible but for substances which are sparingly soluble in water, or where it is desired to remove selectively one component of a food, a non aqueous solvent is employed, the nature of which will depend on the substance or by the operation. Solvent extraction is an important manufacturing operation as, for example, the extraction of oil from oil seeds, the decaffeination of coffee and the preparation of antibiotics. In such operations the solvent is removed as completely as possible from the extracted residue and from the substance which has been extracted. We have not, therefore, concerned ourselves with the solvents used in these processes.

3. On the other hand, the removal of solvent is often undesirable or unnecessary, especially when the solute is susceptible to heat damage as happens with some flavouring matters. The crude natural product is treated with a solvent at relatively low temperatures and the solution used directly for compounding the final flavouring solution. The solvent in this case is an integral part of the food adjunct and ideally should not contribute taste or smell to the adjunct, or to the food flavoured with the adjunct. These considerations apply to the main uses of solvents in the food industry—namely as vehicles for incorporation into food of small quantities of other additives, for example, flavouring agents, colours, antioxidants, essential oils and vitamins or for the dissolution of raw materials or the dilution of concentrated substances. Frequently, the solvent remains in the food and is consumed. These are the solvents dealt with in this report. The prime consideration is that they should be free from toxic hazard, even though the solvent residues in the food as consumed are generally small. The range of solvents should include high- and low-boiling members and, as far as possible, should not contribute either taste or smell to food.

Definition of Solvents

4. For the purposes of this report, we would define solvents as liquid substances, not being natural food substances and the primary use of which is not as flavouring agents, which are capable of facilitating the incorporation of soluble ingredients into prepared food.

5. In its report on Flavouring Agents, the Food Standards Committee recommended that flavouring agents should not at present be controlled by means of a permitted list. We are aware that, if this recommendation is accepted, the definition of solvents in any regulations controlling them will be both difficult and of the greatest importance since it will need to cover all those substances whose essential use is as solvents without having the incidental effect of prohibiting substances whose essential use is as flavourings. We consider that a reasonably effective definition could be based on that set out above and we *recommend* that it should be used as a basis in the preparation of any regulations

resulting from this report. We would define 'natural food substances' in the way it is defined in the Emulsifiers and Stabilisers in Food Regulations, 1962: 'any substance, suitable for use as food and commonly used as food, which is wholly a natural product, whether or not that substance has been subjected to any process or treatment.'

6. Apart from substances already permitted by other additives regulations, we would also *recommend* the exclusion of the following substances from the definition: acetic and lactic acids and propellants.

Evidence

7. A considerable amount of evidence of use was received as a result of the announcement of the review but the toxicity data were far from satisfactory.

8. The following substances were said either to be used or to be likely to be used as solvents in the United Kingdom:

(1) Ethyl alcohol
(2) Glycerol
(3) Propylene glycol (propane-1 : 2-diol)
(4) Diethylene glycol monethylether
(5) isoPropyl alcohol
(6) n-Propyl alcohol
(7) Benzyl alcohol
(8) Glycerol monoacetate
(9) Glycerol diacetate
(10) Glycerol triacetate
(11) Glycerol Ketal (isopropylidene glycerol); (Solketal)
(12) Hexylene glycol
(13) Benzyl benzoate
(14) isoPropyl myristate
(15) Ethyl citrate (triethylcitrate)
(16) Ethyl tartrate
(17) Ethyl acetate
(18) Butyl acetate
(19) Amyl acetate
(20) Butane-1 : 3-diol
(21) Monoglyceride citrate
(22) Sorbitol

9. The first 20 substances were referred by the sub-Committee to its Pharmacology Panel and the 21st was referred by us to our Pharmacology Sub-Committee. We are considering Sorbitol in the course of our review of humectants.

Reports of the Pharmacology Panel and the Pharmacology Sub-Committee

10. The report of the Pharmacology Panel is at Appendix I. We asked our Pharmacology Sub-Committee to consider certain additional evidence and its report is at Appendix II. We accept the findings of these two reports. The fact that the Pharmacology Panel found it necessary to put three substances into the 'possibly toxic' class is a strong argument for the establishment of a permitted list of solvents. We are of the opinion that proper protection of public health

can only be assured by permitted lists for every class of additive for which they are a practical proposition. We therefore *recommend* that only the following solvents should be permitted for use in food:

Ethyl alcohol
Ethyl acetate
Glycerol
Glycerol mono-acetate
Glycerol di-acetate
Glycerol tri-acetate
isoPropyl alcohol
Propylene glycol

We consider that these solvents should fully meet all trade requirements. We *recommend* that the use of isoPropyl Alcohol and Propylene glycol be reviewed in five years' time and that they should then be removed from the permitted list if satisfactory evidence on toxicity has not been received.

Limits

11. In considering the available toxicity data the Pharmacology Sub-Committee were asked to assume that the maximum amount of any solvent left in any food as consumed would not exceed one per cent by weight of the food. We do not consider that there is any need to lay down a statutory limit for the amount of solvent present in a food since solvents are self-limiting and it is unlikely that the figure of one per cent of solvent in a food would be exceeded.

Specifications

12. We *recommend* that any regulations should prescribe specifications of purity for permitted food solvents and that those adopted should wherever possible be based on the monographs in the British Pharmacopoeia.

Labelling

13. We also *recommend* that any solvent for use in food when sold should be labelled so as to indicate its chemical nature, that it is of food quality and conforms to the approved specification. The Food Standards Committee in their Report on Labelling recommended that the statutory declaration should include a statement of the proportion of the essential substances in a compound and the names of the other ingredients in descending order by weight. We endorse these recommendations.

Review

14. We *recommend* that any regulations made as a result of this report should be kept under consideration and reviewed not more than five years after they are made.

Summary of Recommendations

15. (*a*) The addition of solvents as defined in paragraphs 4—6 should be subject to regulations;

(*b*) Ethyl alcohol, ethyl acetate, glycerol, glycerol mono- di- and tri-acetate, isopropyl acetate and propylene glycol should be permitted for use in food (para. 10);

(*c*) Specifications of purity should be laid down (para. 12);

(*d*) Solvents sold for use in food should be appropriately labelled (para. 13);

(*e*) Any regulations made as a result of these recommendations should be reviewed five years after they are made (para. 14).

FAC/REP/2 September 1965

APPENDIX I

THE PHARMACOLOGY PANEL

Report on Solvents

Introduction

1. We were asked to study the information presented for and to report on 20 solvents referred to us by the Food Additives and Contaminants Sub-Committee, under the following names:

Ethyl alcohol
Glycerol
Propylene glycol (propane-1 : 2-diol)
Diethylene glycol monoethylether
isoPropyl alcohol
n-Propyl alcohol
Benzyl alcohol
Glycerol monoacetate
Glycerol diacetate
Glycerol triacetate
Glycerol ketal (isopropylidene glycerol)
Hexylene glycol
Benzyl benzoate
isoPropyl myristate
Ethyl citrate
Ethyl tartrate
Ethyl acetate
Butyl acetate
Amyl acetate
Butane-1 : 3-diol

2. We were provided with data sheets for each of the solvents. These contained information on specification, usage and toxicity received by the Ministry as a result of the Press Notice announcing the Food Standards Committee's Review of Solvents. This was supplemented with information obtained by the Secretariat. We studied the information by comparison with the requirements in our recommendations about Toxicity Tests for Food Additives and Contaminants set out in the Memorandum on Procedure for Submissions on Food Additives and on Methods of Toxicity Testing.

General Observations

3. Information on the composition or purity of the solvents as used in food was totally inadequate. For example, the term "hexylene glycol" can cover a number of isomers; commercial diethylene glycol monoethylether can contain ethylene glycol. Suitability for use in food can only be properly assessed when the results of toxicity studies can be related to products of defined and commercially reproducible quality. Only those solvents which can be prepared to fulfil a detailed specification should be permitted.

4. British Pharmacopoeia 1963 (B.P. 1963), British Pharmaceutical Codex 1963 (B.P.C. 1963) monographs and British Standards Institution standards are available (as shown below). These monographs and standards were not made for application to solvents for use in food. Some, it will be noted, are specifically for use as analytical reagents. The monographs and standards would, however, probably provide a basis for further study.

Solvent	Description in Monograph or Standard	Monograph or Standard
Ethyl alcohol	Alcohol (95 per cent) Dehydrated alcohol Ethyl alcohol (Ethanol)	B.P. 1963 B.P. 1963 B.S. 507
Glycerol	Glycerin Chemically Pure Glycerin	B.P. 1963 B.S. 2625
Propylene glycol	Propylene glycol	B.P. 1963
Diethylene glycol monoethylether	—	—
isoPropyl alcohol	isoPropyl alcohol isoPropyl alcohol (isopropanol)	B.P. 1963 B.S. 1595
n-Propyl alcohol	n-Propyl alcohol	B.P. 1963 (Reagent grade only)
Benzyl alcohol	Benzyl alcohol Benzyl alcohol	B.P. 1963 B.S. 3D7 (aircraft use)
Glycerol monoacetate	—	—
Glycerol diacetate	Diacetin	B.S. 1594
Glycerol triacetate	Triacetin Triacetin	B.P. 1963 (Reagent grade only) B.S. 1997
Glycerol ketal	—	—
Hexylene glycol	—	—
Benzyl benzoate	Benzyl benzoate	B.P. 1963
isoPropyl myristate	isoPropyl myristate	B.P.C. 1963
Ethyl citrate	—	—
Ethyl tartrate	—	—
Ethyl acetate	Ethyl acetate Ethyl acetate	B.P. 1963 (Reagent grade only) B.S. 553
Butyl acetate	Butyl acetate	B.S. 551
Amyl acetate	Amyl acetate	B.S. 552
Butane-1:3-*diol*	—	—

5. Little information was provided on the individual usage or levels of use of the various solvents. In the absence of adequate information on specifications or usage, we have considered the available toxicity data assuming that:

(*a*) the solvents would be suitable for use in food,

(*b*) the maximum amount of any solvent left in any food as consumed would not exceed one per cent by weight; and (*c*) any further toxicological studies should be made on solvents of defined and commercially reproducible purity.

6. We then grouped the solvents into five classes, namely,

(*a*) solvents that the available evidence suggests are acceptable for use in food;

(*b*) solvents that on the available evidence may be regarded as provisionally acceptable for use in food meantime but about which further information is necessary and which must be reviewed within a specified period of time;

(*c*) solvents for which the available evidence suggests possible toxicity and which ought not to be allowed in food without evidence establishing their acceptability;

(*d*) solvents for which the available evidence was inadequate to enable an opinion to be expressed as to their suitability for use in food; and

(*e*) solvents for which no information on toxicity was available.

Detailed Observations

7. Information about acute oral toxicity to animals was available for all solvents except glycerol ketal, ethyl tartrate and amyl acetate, but information about the results of short-term and long-term studies, including carcinogenicity, was either totally lacking or grossly inadequate.

8. (*a*) *Solvents that the available evidence suggests are acceptable for use in food*

Ethyl alcohol and *Glycerol* were accepted as traditional food ingredients.

Ethyl acetate and the *Acetins* (glycerol mono-, di-, and tri-acetates) were also regarded as acceptable on the basis that they would probably be metabolised by the same route as ethyl alcohol or glycerol, and acetic acid.

(*b*) *Solvents that on the available evidence may be regarded as provisionally acceptable for use in food meantime but about which further information is necessary and which must be reviewed within a specified period of time.*

(i) *isoPropyl alcohol.* There are some results of metabolic studies in man (1)(2). There seem to be no results of studies with animals of longer duration than one year. Female rats drinking 1 per cent and 5 per cent aqueous solutions of isopropyl alcohol for 27 weeks showed some depression in growth (3). Injection and inhalation experiments of up to a year's duration suggest that isopropyl alcohol is not carcinogenic for mice (4). In view of the long-standing use of isopropyl alcohol as a food solvent, we are prepared to regard it as provisionally acceptable, at levels in food as consumed of not more than 1 per cent; we deem it essential that long-term feeding studies with isopropyl alcohol, particularly in relation to carcinogenicity, will be undertaken and completed within a time to be specified.

(ii) *Propylene glycol.* Groups of 10 rats were fed for two years with diets containing 2·45 per cent or 4·9 per cent propylene glycol, the higher level corresponding to a daily intake of about 2 ml/kg body-weight. Apart from slight chronic liver damage at the levels tested, there were no effects attributable to the propylene glycol (5). Daily feeding of 5 per cent propylene glycol, in drinking water, to 4 dogs for 5 to 9 months, corresponding to a daily intake of 5·1 ml. per kg body-weight caused neither toxic effects nor pathological and functional changes of liver and kidneys, although the average concentration of propylene glycol in the blood ran as high as 325 mg per 100 ml. Concentrations of 10 per cent in drinking water caused the dogs to become thirsty and to drink more so that the average concentration of propylene glycol in the blood rose to 800 mg per 100 ml. The dogs then died of marked depression of the central nervous system or of a subsequent pneumonia (6). We note that propylene oxide, from which propylene glycol may be prepared, has been shown to be a carcinogen (7); this emphasises the need for a proper specification. We agreed that this solvent is provisionally acceptable for use in food but that further long-term toxicological studies are required.

(*c*) *Solvents for which the available evidence suggests possible toxicity and which ought not to be allowed in food without evidence establishing their acceptability.*

(i) *Diethylene glycol monoethylether.* We noted that commercial grades may contain up to 30 per cent ethylene glycol and that traces of the latter may be present even in the so-called "pure" product (8). A level of 2·16 per cent in the diet of 10 rats for 2 years gave testicular and slight liver damage and, in one rat, a renal calculus (5). After rat studies with "pure" solvent in drinking water at a level of 1 per cent and mouse studies with "pure" solvent at 5 per cent in the diet, no conclusions could be drawn about survival rates compared with controls after about 2 years, but there were signs of renal damage (9). We agreed, from the evidence presented, that diethylene glycol monoethylether ought not to be allowed in food and concluded that any further evidence, if submitted, must relate to a product of defined and commercially reproducible purity.

(ii) *Hexylene glycol.* Further information is required about the precise formula or composition of this solvent. Rats given daily doses of 0·08g/kg body-weight of hexylene glycol for six weeks (the lowest level fed) showed evidence of kidney damage at post-mortem (10). No results of long-term studies were available.

(iii) *Ethyl citrate.* We noted, with some surprise, a report that ethyl citrate had a toxic effect on the central nervous system of cats (11); but because of the vulnerability of man to this type of damage we have felt compelled to place this substance in class (c). No results of long-term studies were available and further work is therefore desirable.

(*d*) *Solvents for which the available evidence was inadequate to enable an opinion to be expressed as to their suitability for use in food.*

(i) *n-Propyl alcohol*
(ii) *Benzyl alcohol*
(iii) *isoPropylidene glycerol*
(iv) *Benzyl benzoate*
(v) *isoPropyl myristate*
(vi) *Butyl acetate*
(vii) *Amyl acetate*
(viii) *Butane*-1 : 3-*diol*

The results of short-term and long-term studies are required for these seven solvents.

(*e*) *Solvents for which no information on toxicity was available*

(i) Diethyl tartrate

Summary of Classification

9. (*a*) *Solvents that the available evidence suggests are acceptable for use in food*

Ethyl alcohol
Glycerol
Ethyl acetate
Glycerol mono-, di- and tri-acetates

(*b*) *Solvents that on the available evidence may be regarded as provisionally acceptable for use in food meantime, but about which further information is necessary and which must be reviewed within a specific period of time*

isoPropyl alcohol
Propylene glycol

(*c*) *Solvents for which the available evidence suggests possible toxicity and which ought not to be allowed in food without evidence establishing their acceptability*

Diethylene glycol monoethylether
Hexylene glycol
Ethyl citrate

(*d*) *Solvents for which the available evidence was inadequate to enable an opinion to be expressed as to their suitability for use in food.*

n-Propyl alcohol
Benzyl alcohol
isoPropylidene glycerol
Benzyl benzoate
isoPropyl myristate
Butyl acetate
Amyl acetate
Butane-1 : 3-diol

(*e*) *Solvents for which no information on toxicity was available*

Diethyl tartrate

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(10) Unpublished Report from Distillers Co., Ltd.

(11) Finkelstein and Gold.
Toxicol. Appl. Pharmacol., **1**, 283 (1959).

PHARMACOLOGY SUB-COMMITTEE

Report on the Solvents, Diethylene Glycol Monoethylether, Benzyl Alcohol, Triethyl Citrate and Monoglyceride Citrate

Diethylene glycol monoethylether

1. In their Report on Solvents (Appendix I), the former Pharmacology Panel agreed, from the evidence presented, that diethylene glycol monoethylether ought not to be allowed in food and concluded that any further evidence must relate to a product of defined and commercially reproducible purity. In addition to the evidence available to the former Pharmacology Panel, we were supplied with

(i) the British Industrial Biological Research Association's Report on, and Interpretative Summary of, an 11-week study on rats fed diets containing 0·25 per cent, 1·0 per cent or 5·0 per cent of diethylene glycol monoethylether [BIBRA Research Report 3/1964];

and (ii) the summary of an unpublished study by Smyth, Carpenter and Shaffer on rats which received diethylene glycol monoethylether in their drinking water for 2 years. The daily intakes of solvent corresponded to approximately 0·95, 0·20, 0·04 and 0·01 g./kg. body-weight. [BIBRA Bulletin **3**, 409 (1964)].

2. The diethylene glycol monoethylether tested by the British Industrial Biological Research Association was stated to contain 0·4 per cent ethylene glycol. The purer of the two grades of diethylene glycol monoethylether tested by Smyth and others contained less than 0·2 per cent ethylene glycol. We were not however provided with a full commercial specification for diethylene glycol monoethylether.

3. We agreed not to give further consideration to diethylene glycol monoethylether until we were provided with a full submission which included both a proper commercial specification and the results of toxicity studies on material complying with this specification.

Benzyl alcohol

4. No toxicological information additional to that available to the former Pharmacology Panel was supplied. For example, there was no information about long-term toxicity. We confirmed the former Pharmacology Panel's view that the available toxicological evidence was inadequate to enable an opinion to be expressed as to the suitability of benzyl alcohol when used as a solvent in food.

Triethyl citrate

5. The former Pharmacology Panel had noted, with some surprise, the reported adverse effect that triethyl citrate had on the central nervous system of cats [Finkelstein and Gold, Toxicology and Applied Pharmacology, **1**, 283, (1959)]. We studied this report and confirmed that the available evidence, rather surprisingly, suggested possible toxicity. We think that further information is needed to explain this adverse effect of triethyl citrate in cats.

Monoglyceride citrate

6. The initial representation to the Food Additives and Contaminants Committee requested the inclusion of glycerol monocitrate on any permitted list of solvents since there was no alternative material which would adequately disperse the oleo-resin of white pepper. A subsequent request for further information, to those submitting the representation, revealed that the solvent concerned was monoglyceride citrate and not glycerol monocitrate; though, as will be seen in the next paragraph, the term 'monoglyceride citrate' is not an accurate nomenclature.

7. Monoglyceride citrate was stated to be prepared by reacting distilled glyceryl mono-oleate with anhydrous citric acid for 4 hours at 128°C—130°C. The composition of a typical batch was given as:

Glycerol mono-oleate	59·5%
Glycerol mono-oleate mono-citrate	33·5%
Glycerol mono-oleate di-citrate	0·6%
Citric acid	3·1%

and the following specification was proposed:

Saponification value	260—265
Acid value	70—100
Iodine number	53—60
Refractive index	1·4660—1·4680
Heavy metals (including arsenic and lead)	less than 1 p.p.m.

No indication is given of the range in composition to be expected from different batches and the data show that only 96·7 per cent of the material is accounted for in the analysis of the typical batch.

We also noted that monoglyceride citrate of the composition given comes within the definition for permitted partial glycerol esters given in the Emulsifiers and Stabilisers in Food Regulations, 1962.

8. The submission stated that monoglyceride citrate would be present in white pepper extract at approximately a 4 per cent level and that the usage of the pepper would determine the level in the food. For example, in sausage, with a relatively high pepper level, the monoglyceride content would be about 200 p.p.m. The U.S. Food Additive Regulations 21 CFR 121·1036 allow the use of monoglyceride citrate as a synergist and solubiliser for antioxidants at levels of up to 200 p.p.m. in oils and fats.

9. The evidence for the safety of monoglyceride citrate was based on *in vitro* enzyme digestibility studies purporting to show that digestion of monoglyceride citrate proceeded as rapidly as or more rapidly than that of corn oil or of glyceryl lactopalmitate and that the digestion products were citric acid, glycerol and fatty acid; also that *in vivo* studies with rats demonstrated almost complete digestion and absorption of monoglyceride citrate. No results of long-term studies were provided.

10. We agreed that the toxicological evidence provided was inadequate to enable an opinion to be expressed as to the suitability of monoglyceride citrate for use in food.

General Comment

11. We were handicapped in our study by having to consider, as food additives, substances which were not properly specified (e.g. diethylene glycol monoethylether) or which could not be specifically characterised (e.g. monoglyceride citrate). If a substance cannot be specifically characterised we think that information should be provided on the purity of the ingredients used and on the range of products produced by the process described. In either case, the toxicological information provided must take account of the range in composition to be expected of the additive as commercially available for use in food unless it can be convincingly demonstrated that such variation is irrelevant.

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